REMARKS

Claims 1 - 27 are currently pending in the application. Claims 10 – 25 are withdrawn from consideration. No claims have been amended. New claims 28 and 29 have been added. No new matter has been added. Support for the new claims can be found throughout the specification, for example in the Amendment to the Specification made 5/25/2004, the paragraph on page 11 beginning at line 12.

Specification

The Examiner has requested a new sequence listing in compliance with 37 CFR 1.821 through 1.825. The Examiner argues that the Application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because the sequences that appear on page 6 (lines 5 ,7 ,8 ,9) and page 13 (lines 1, 3, 4, and 5) are not present in the sequence listing, Applicants direct the Examiner to the Amendment submitted on 27 May 2004. In the Amendment dated 27 May 2004, Applicants amended the specification to include SEQ ID NOs for the above-mentioned sequences appearing on pages 6 and 13. In the Amendment dated 27 May 2004 Applicants provided a Sequence Listing that includes these sequences. Applicants kindly request that the Examiner consider this Amendment and withdraw the improper objection.

Drawings

The Examiner has requested new corrected drawings in compliance with 37 CFR 1.21(d). Applicants are submitting corrected drawings in reply to the Office Action.

Rejection of Claims 1 – 9, 26 and 27 Under 35 U.S.C. §103(a)

Claims 1 – 9, 26 and 27 are rejected under 35 U.S.C. §103(a) as being unpatentable over Kay et al. (US Patent No 5,747,334; "the '334 patent") in view of Thornberg et al. (US Patent No 5,939,288; "the '288 patent"), Puig et al.(Methods. 2001); Laible et al. (US Patent Application No. 20020102655; "the '655 Application"); Keefe et al. (Prot. Exp. And Purif. 2001); Stofko-Hahn et al.(FEBS 1992); and Zheng et al.(Gene 1997).

The Office Action alleges that the '334 patent teaches DNA encoding Totally Synthetic Affinity Reagents (TSARs), which comprise polypeptides having one or more specific binding domains. The Office Action argues that the '288 patent teaches using multiple affinity tags to facilitate purification. The Office Action argues that Puig et al. teaches the Tandem Affinity Purification (TAP) method of purifying protein using two IgG binding domains and a calmodulin binding peptide. The Office Action argues that Laible et al. teaches it is conventional to use multiple affinity tags. The Office Action argues that Keefe et al. teaches purification of proteins using SBP tag. The Office Action alleges Stofko-Hahn teaches purification of a protein using CBP tag. The Office Action argues that Zheng et al. teaches that use of CBP tag at the C-terminus enhances target protein expression. The Office Action argues that it would have been obvious for one of skill in the art to combine all the above references and use multiple affinity tags for protein purification because the cited references teach affinity tags for protein purification and why they are useful and advantageous. Applicants disagree and respectfully traverse the rejection.

According to MPEP 2143.01, "'In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification.' *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

The instant claims recite an isolated polynucleotide comprising at least two tag sequences, wherein one of said two tag sequences encodes streptavidin-binding peptide having a nucleotide sequence presented in Figure 1. These claims differ from the cited art for the following reasons.

The '334 patent relates to Totally Synthetic Affinity Reagents (TSARs) with specific binding properties. According to the '334 patent, TSARs comprise at least two functional

regions: a binding domain and an effector portion. The different functional regions of a TSAR are illustrated in Figure 7, and described in column 4, wherein a TSAR:

> is intended to encompass a concatenated heterofunctional protein, polypeptide and/or peptide that includes at least two distinct functional regions. One...is a binding domain with affinity for a ligand. A second...is an effector domain that is biologically or chemically active to enhance expression and/or detection and/or purification of the TSAR (column 4; emphasis added).

The '334 patent teaches that the binding domain of the TSARs can include multiple binding domains; however there is no teaching that the binding domains be two <u>different</u> binding domains. In fact, the inclusion of multiple copies of the same binding domain would be favored according to the teaching of the '334 patent because inclusion of multiple copies would increase the affinity, i.e. the strength and stability of binding. The Examiner's attention is drawn in particular to column 4, lines 31 – 36, which states that:

> One region of the heterofunctional TSAR molecule is a binding domain with affinity for a ligand, that is characterized by 1) its strength of binding under specific conditions, 2) the stability of its binding under specific conditions and 3) its selective specificity for the chosen ligand.

This language is repeated at col. 36, lines 60 – 65, and emphasizes that binding strength and stability of binding are important for the function of the TSAR molecule. One of skill in the art understands that affinity can be increased by multimerizing a binding domain (i.e. by including multiple copies of the <u>same</u> binding domain). At column 8, lines 47 – 55 of the '334 patent, the specification further supports the idea that multimers of the <u>same</u> binding domain are advantageous:

> The TSARs can also have in vitro a utility similar to monoclonal antibodies or other specific binding molecules for the detection, quantitation, separation or purification of other molecules. In one embodiment, a number of TSARs or the binding domains thereof can be assembled as multimeric units to provide multiple binding domains that have the *same specificity* and can be fused to another molecule that has a biological or chemical activity. (emphasis added)

In fact, there is no teaching or suggestion of multiple binding domains of <u>different</u> specificities, nor is there any teaching or suggestion that the inclusion of multiple binding domains would even have any advantage in a TSAR construct.

The '334 patent only teaches TSAR constructs individually binding streptavidin (col. 64 – 66) or calmodulin (col. 67 – 71), or polystyrene (col. 66 67), dyenin (col. 71 – 72), vinculin (col. 72 – 73), or glutathione –S-transferase (col. 73 – 74). As mentioned above, there is no teaching or suggestion for combining multiple binding domains of different specificities in a TSAR construct. "It is insufficient that the prior art disclosed the components of the patented device, wither separately or used in other combinations; there must be some teaching, suggestion, or incentive to make the combination made my the inventor (*Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed Cir. 1985)*)." In the case of Smithkline Laboratories v Helena Corporation, *859 F.2d 878; 1988 U.S. App. LEXIS 13995; 8 U.S.P.Q.2D (BNA) 1468*, it was indicated that:

> Helena cannot pick and choose among the individual elements of an assorted prior art references to recreate the claimed invention. Helena has the burden to show some teaching or suggestion in the references to support their use in *the particular claimed combination. Uniroyal Inc., 837 F.2d at 1051, 5 USPQ2d at 1438-39.*[emphasis added]

The only example provided in the '334 patent is to TSARs with single binding specificity. Therefore, Applicants submit that the '334 reference as a description of "multiple binding domains" in TSARs does not teach or suggest constructs in which there are two different binding domains, and particularly not a TSAR with a streptavidin binding peptide encoded by a nucleotide sequence presented in Figure 1 or a TSAR with a calmodulin binding peptide (CBP) and a streptavidin binding peptide (SBP). Moreover, the '334 patent does not teach a SBP, but rather a polypeptide selected from a randomized peptide library that binds streptavidin.

Claims 1 – 9, 26 and 27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over the '334 patent in view of Thornberg et al. (US Patent No 5,939,288; "the '288 patent"), Puig et al. (Methods. 2001), Laible et al. (US Patent Application No. 20020102655; "the '655 Application"), Keefe et al. (Prot. Exp. And Purif. 2001), Stofko-Hahn et al. (FEBS 1992); and Zheng et al. (Gene 1997). Applicants respectfully traverse the rejection.

There is no teaching in any of the Thornberg et al., Puig et al., Laible et al., Keefe et al., Stofko-Hahn et al., and Zheng et al. references that cures the defects of the '334 patent, and whereby the instant that claims recite an isolated polynucleotide comprising at least two tag

sequences, wherein one of said two tag sequences encodes streptavidin-binding peptide having a nucleotide sequence presented in Figure 1, would be considered obvious.

The flaws of the '334 patent have been described above. The Thornberg et al., Puig et al., Laible et al., Keefe et al., Stofko-Hahn et al., and Zheng et al. references do not render the rejected claims obvious. The combination of the references fails to teach or suggest, "an isolated polynucleotide comprising at least two tag sequences, wherein one of said two tag sequences encodes streptavidin-binding peptide having a nucleotide sequence presented in Figure 1." The combination also fails to teach or suggest an isolated polynucleotide comprising at least two tag sequences, wherein one of the tag sequences encodes SBP and wherein one of the tag sequences encodes CBP. In particular, the references never teach any advantage or motivation to combine the two particular tag sequences. The '288 patent teaches purified signal peptides wherein the signal peptide facilitates secretion of at least one protein from a plant cell into secretory material. In reference to affinity tags, the '288 patent teaches attachment of an affinity tag to the expressed protein to facilitate purification (e.g. FLAG tag, polyhistidine; column 6 line 55). The '288 patent teaches affinity tags ligated between the signal peptide and the multiple cloning site. The '288 patent merely provides systems and schemes for affinity tag attachment, and does not teach or suggest, in combination with the '334 patent, "an isolated polynucleotide comprising at least two tag sequences, wherein one of said two tag sequences encodes streptavidin-binding peptide having a nucleotide sequence presented in Figure 1." Applicants respectfully request withdrawal of the rejection and allowance of the claims.

The Examiner argues that the Puig reference teaches the Tandem Affinity Purification (TAP) method of purifying protein using as the tag the combination of two IgG binding domains and a calmodulin binding peptide. The Puig reference uses a method that combines purification of the protein complex of interest using two different affinity tags, CAM binding peptide and two IgG binding domains, fused to at least one known protein component of a complex of interest by genetic methods. The use of two consecutive purification steps allows for isolation of the complex, in a purified form, without disruption of the targeted complex. However, the Puig reference differs from the instant claims in that only certain specific combinations of purification tags are suitable for this method: IgG binding domains and calmodulin binding peptide. The Puig reference does not teach or suggest using SBP as taught by the instant claims.

The Examiner argues that Laible et al. (US Patent Application No. 20020102655) teach that it is conventional to use multiple affinity tags. The '655 application uses affinity tags to facilitate extraction of protein from the membrane environment of photosynthetic organisms. The '655 application teaches heterologous membrane protein purification through isolation of the heterologous membrane protein from other intracytoplasmic membrane (ICM) compartments using an affinity tag engineered into the protein-coding sequence. "The affinity tag is used to readily sequester the heterologous membrane proteins in native form by chromatography with the correspondingly compatible resin [0178]." The affinity tag(s) of the '655 application are specifically directed to removing the protein complex from the ICM compartment, and as such, all teachings of the '655 application are directed to this use. The '655 application does not teach or suggest the use of a SBP or CBP affinity tag in the methods of the invention, and moreover there is no teaching or suggestion that either a SBP or CBP affinity tag or both would be suitable for the methods of the '655 application.

The Examiner argues that Keefe et al. teach the purification of proteins with the SBP tag. Further, the Examiner argues that Stofko-Hahn et al. teach purification of a protein using the CBP tag. The Examiner argues that Zheng et al. teach that use of the CBP tag at the C-terminus enhances expression of the target protein.

However, taken together, Keefe et al., Stofko-Hahn et al. and Zhang et al. do not teach an isolated polynucleotide comprising at least two tag sequences, wherein one of said two tag sequences encodes streptavidin-binding peptide having a nucleotide sequence presented in Figure 1. There is nothing in the art cited that would lead one of ordinary skill in the art to select a SBP having a nucleotide sequence presented in Figure 1, nor is there anything in the art cited that would lead one of ordinary skill in the art to select the combination of SBP and CBP.

The Office Action does not point to any specific passages in the cited references which provide motivation to combine those references, nor to any other sources for such motivation. Rather, it relies on statements that "it would have been obvious . . . to modify the method" of the references to produce Applicants' invention. It has not been stated with any specificity, beyond general statements that multiple affinity tags are advantageous, and why one of ordinary skill in the art at the time the invention was made would be motivated to combine the cited references and passages therein in the particular manner to produce Applicants' claimed invention.

The MPEP states that:

> "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a prima facie case of obvious [sic] was held improper.). The level of skill in the art cannot be relied upon to provide the suggestion to combine references. Al-Site Corp. v. VSI Int'l Inc., 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

MPEP § 2143, and that

> "In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." In re Linter, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

The Office Action must therefore state why one of ordinary skill would be motivated to combine the references, e.g., from the references themselves, from the knowledge of one of ordinary skill, or the nature of the problem to be solved. "[T]he references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious" (Ex parte Clapp, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985)). The mere fact that references can be combined does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination. Berghauser v. Dann, Comr. Pats., 204 U.S.P.Q. 393 (Dist. DC 1979); ACS Hospital Systems, Inc. v. Montefiore Hospital, 221 U.S.P.Q. 929 (Fed. Cir. 1984). Citing references which merely indicate that isolated elements and/or features recited in the claims are known is not a sufficient basis for concluding that the particular combination of claimed elements would have been obvious. Ex parte Hiyamizu, 10 U.S.P.Q.2d 1393 (Bd. Pat. App. & Inter. 1988).

The Office Action has failed to provide motivation for combining the references of Kay et al. in view of Thornberg et al., Puig et al., Laible et al., Keefe et al., Stofko-Hahn et al., and Zheng et al., and has also failed to establish that the cited references disclose Applicants' invention. Applicants respectfully request that that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Rejection of Claims 1 – 9, 26 and 27 Non-Statutory Double Patenting

Claims 1 – 9, 26 and 27 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 13, and 21 of copending Application No. 10/ 987,388.

Applicants note that they will file a terminal disclaimer, if appropriate, once otherwise allowable subject matter has been determined in the present application.

CONCLUSION

In view of the above amendments and remarks, Applicant believes the pending application is in condition for immediate allowance. Any additional fee occasioned by this paper may be charged, or overpayment credited to, Deposit Account 04-1105, Reference No. 225436/2465.

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